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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/576,653	11/16/2006	Wei Cheng	05-937-B5	5425

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EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/576,653	CHENG ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-20,29 and 34-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13-20,29 and 34* is/are allowed.

6)☒ Claim(s) *35-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Withdrawal of Final Rejection

The Final Rejection of Nov. 25, 2008 is withdrawn to revise the previous incorrect Lack of Unity, to act on previously incorrectly withdrawn claims and to enter the following new grounds of rejection. Accordingly, Applicants' submission of Feb. 25, 2009 is entered as a matter of right.

Lack of Unity

The Lack of Unity requirement set forth in the Office Action of Feb. 5, 2008 is seen to have been in error. No restriction should have been required between Groups I-III, on the one hand, and Groups IV-XII, on the other hand. Accordingly, the Lack of Unity is revised as follows:

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

I. Claims 1-12 and 34-36 (of the original claims), drawn to compounds of Formula I where only one of B, D and E is N, classified in class 546, subclasses 268.1, 286, 287, 288, 289 and 290, *inter alia*, a pharmaceutical composition thereof, a metabolite thereof, claims 37-40 and 42, drawn to a method of modulating *in vivo* activity of a kinase, claim 41, drawn to a screening method for a p70S6 kinase

modulator, claim 43, drawn to a method of inhibiting abnormal metabolic activity in a cell, all classified in class 514, subclasses 336, 344, 345, 349, 350, 351 and 352, *inter alia*.

II. Claims 13-20, 29 and 34-36 (presently pending claims), drawn to compounds of Formula I where only two of B, D and E are N, classified in class 544, subclasses 297, 298, 309, 322, 323, 334 and 335, *inter alia*, a pharmaceutical composition thereof, and a metabolite thereof, claims 37-40 and 42, drawn to a method of modulating the *in vivo* activity of a kinase, claim 41, drawn to a screening method for a p70S6 kinase modulator, claim 43, drawn to a method of inhibiting abnormal metabolic activity in a cell, all classified in class 514, subclasses 256, 269, 272, 274 and 275, *inter alia*.

III. Claims 1, 2 and 34-36 (of the original claims), drawn to compounds of Formula I where all three of B, D and E are N, classified in class 544, subclasses 194, 204, 211 and 212, *inter alia*, a pharmaceutical composition thereof, and a metabolite thereof, claims 37-40 and 42, drawn to a method of modulating the *in vivo* activity of a kinase, claim 41, drawn to a method of screening for a p70S6 kinase modulator, claim 43, drawn to a method of inhibiting abnormal metabolic activity in a cell, all classified in class 514, subclasses 241 and 245, *inter alia*.

Rejections Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. The specification does not reasonably enable a method using a compound of claim 13 to modulate *in vivo* activity of a kinase (claim 37), where the kinase is p70S6K (claim 38), by inhibiting p70S6K (claim 39), to treat disease or disorder associated with uncontrolled, abnormal or unwanted cellular activities (claim 40), to screen for a p70S6 kinase modulator (claim 41), to inhibit cell proliferative activity (claim 41) or inhibit abnormal cell metabolic activity (claim 43).

The specification asserts the claimed compounds inhibit, regulate or modulate kinase or p70S6K activity and are therefor of value in the above recited conditions, for which insufficient enablement is provided. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, 66 FR 1092-1099 (2001), emphasizing "a claimed invention must have a specific and substantial utility." MPEP 2163, *et. seq*. This disclosure is insufficient to enable the claimed methods based on the disclosed PDE2 inhibition.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed. Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the compounds. The claims cover methods using substituted pyrimidine compounds.

(b) Scope of the conditions covered. The claims cover methods to treat above conditions said to be responsive to inhibition, regulation or modulation of kinase signal transduction.

Modulate kinase activity *in vivo*. Kinases (phosphotransferase) are enzyme types that transfer phosphate groups from high-energy donor molecules, e.g., ATP, to specific target molecules (substrates); the process is termed *phosphorylation*. An enzyme that *removes* phosphate groups from targets is known as a phosphatase. One of the largest kinase groups are protein kinases, which act on and modify activity of specific proteins, transmit signals and control complex cell processes. Up to 518 different human kinases have been identified. Various other kinases act on small molecules (lipids, carbohydrates, amino acids, nucleotides, and more), either for signaling or to prime them for biochemical reactions in metabolism.

Modulate p70S6K activity *in vivo*. p70 ribosomal protein S6 kinase (p70S6K) participates in protein synthesis control and activates in response to hormones, mitogens and nutrients. It phosphorylates the 40S ribosomal protein S6, which is involved in translation of certain mRNAs, the 5'-TOP mRNAs encoding ribosomal proteins and elongation factors. p70S6K is activated by insulin in muscle, but not in hepatocytes. In these cells, p70S6K is activated by amino acids like glutamine and leucine, which act synergistically. However, crosstalk between insulin and amino acids can be demonstrated with leucine, which enhances insulin signaling towards p70S6K in many cell types, including hepatocytes.

The mechanism of p70S6K activation involves a complex sequence of multiple serine/threonine phosphorylations catalyzed by several protein kinases. One of these is the mammalian target of rapamycin (mTOR), which phosphorylates p70S6K on Thr389 and is inhibited by the immunosuppressant rapamycin. Phosphorylation

of this site correlates with kinase activity. mTOR may also phosphorylate and thereby inactivate a protein phosphatase that in turn inactivates p70S6K. The amino-acid signaling pathway leading to p70S6K activation may comprise inhibition of protein phosphatase. Whatever the activation mechanism of p70S6K by mTOR, the latter plays an essential role, because p70S6K activation caused by almost all stimuli is inhibited by rapamycin. Phosphorylation of Ser411, Thr421 and Ser424, which are within a Ser-Pro rich region located in the autoinhibitory domain, is also thought to modulate p70S6K activity. In response to insulin, 3-phosphoinositide-dependent protein kinase (PDK1) is directly involved in p70S6K activation. Target phosphorylation site for PDK1 is Thr229 in the p70S6K catalytic domain.

Acetyl-CoA carboxylase (ACC) is a regulatory enzyme in fatty acid synthesis. In liver cells ACC activation is correlated with cell swelling induced by amino acids cotransported with Na^+ or by hypotonic medium. ACC activity is controlled by various mechanisms, including changes in the degree of polymerization, allosteric regulation by citrate and glutamate and covalent modification by phosphorylation/dephosphor-ylation. The active form is generally assumed to be dephosphorylated, although phosphorylation has been invoked to explain ACC activation by insulin in adipocytes.

Under stress conditions, such as anoxia or inhibition of mitochondrial oxidative phosphorylation, ATP balance becomes negative and the AMP/ATP ratio increases. This leads to AMP-activated protein kinase (AMPK) activation, which functions as a metabolic master switch and inhibits anabolic processes, preserving ATP. ACC is phosphorylated *in vitro* by AMPK on Ser79, Ser1200 and Ser1250, the

phosphorylation of Ser79 being responsible for inactivation. AMPK-inactivated ACC can be reactivated by a glutamate-dependent type-2A protein phosphatase (GAPP), which dephosphorylates a synthetic peptide encompassing the Ser79 phosphorylation site for AMPK in ACC. In hepatocytes the activation ACC state is expected to result from balance between GAPP and AMPK activities, although involvement of other protein kinase or phosphatases has not been ruled out.

Because ACC and p70S6K display a similar and parallel pattern of activation in hepatocytes incubated with glutamine, the question arises whether there is also a common mechanism for inactivation. It is indeed expected that ACC and p70S6K, which control energy-consuming biosynthetic pathways, are less active when ATP supply becomes limiting. The effect of different AMPK activators and the effect of protein phosphatase inhibitors the amino-acid-induced ACC and p70S6K activation were examined in freshly prepared rat hepatocytes. Results show that ACC and p70S6K activation depend on protein phosphatase and both enzymes may be inactivated under conditions leading to AMPK activation.

Uncontrolled, abnormal or unwanted cellular activities. In *polycythemia vera*, uncontrolled and rapid cellular reproduction and maturation cause proliferation or hyperplasia of all bone marrow cells. The cause of such uncontrolled cellular activity is probably due to a multipotential stemcell defect. A genetic predisposition with inadequate immune responses and uncontrolled cellular activity may make some women more susceptible to cervical cancer. Dreams are caused mostly by uncon--trolled cellular activity. A benign tumor is any abnormal cellular growth that remains

confined to one area, is not cancerous and does not spread to distant body areas. Abnormal cellular activity is often one predisposing factor for human osteosarcoma. Inflammation and gene expression can be considered unwanted cellular activities.

Inhibition of cell proliferative activity. Mild intracellular redox imbalance inhibits cell proliferation independent of reactive oxygen species generation. Inhibition of the growth of hepatocellular carcinoma has been attributed to a decrease of cell proliferative activity. Indole-3-carbinol selectively inhibits cell proliferative activity induced by estradiol in responsive human breast cancer cells and phosphorylation of the estrogen receptor. CD54 and CD106 are involved in the ability of follicular dendritic cells to inhibit T-cell proliferative responses. Conjugated linoleic acid may act by antioxidant mechanisms, prooxidant cytotoxicity, inhibition of nucleotide and protein synthesis, reduction of cell proliferative activity and inhibition of both DNA-adduct formation and carcinogen activation. In male Syrian hamsters, stress influences epidermal cell proliferative activity and sebaceous gland activity.

Inhibition of abnormal cell metabolic activity. Increasing oxygen delivery to the myocardium so that the mitochondria can make more ATP via aerobic mechanisms and/or by decreasing heart rate and arterial blood pressure and thus, the rate of ATP breakdown by tissue, are pharmacologic therapies aimed at reducing abnormal cell metabolism to treat chronic stable angina.

The specification fails to identify treatment results with methods of this invention and how to recognize such results. Each of the above conditions has various symptoms and there is no indication of which specific symptoms are alleviated.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

   Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

   > The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

   Plant Genetic Systems v. DeKalb Genetics Corp., 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claim.

4. **State of the prior art:** The art indicates the need for undue experimentation.

   The anti-proliferative effects of sirolimus (rapamycin, a p70S6K inhibitor) may have a role in treating cancer, but Rapamycin shows no effect on its own. Doxorubicin and sirolimus combination therapy has been shown to drive AKT-positive lymphomas into remission in mice. Bcl-2-positive lymphomas were completely resistant to sirolimus therapy; nor are eIF4E expressing lymphomas sensitive to sirolimus. As with all immunosuppressive medications, rapamycin decreases the body's inherent anti-cancer activity and allows some cancers to proliferate, which

would otherwise have been naturally destroyed. Wikipedia, Sirolimus, updated 02/28/2009, <http://en.wikipedia.org/wiki/Sirolimus>, downloaded 3/19/2009.

Sawyers, et al., Nature Reviews – Cancer, Mar. 2008, Vol. 8, studying rapamycin use in renal cancer treatment, detected that rapamycin delivery to tumor cells is impaired in some patients and concluded, "This trial shows the importance of investigating drug delivery to tumour cells and target modulation in patients to guide future clinical development of targeted agents. Further study of rapamycin in PTEN-deficient glioblastoma is warranted."

Ability of any and all kinases or a p70S6K inhibitor to effectively treat all conditions encompassed by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests of all recited conditions the claims encompass. Applicants do not provide competent evidence that the instantly disclosed tests are highly predictive for all uses covered embraced by claim language for all intended hosts.
6. **Skill of those in the art:** Wikipedia and Sawyers call into question treatment with the claimed methods and confirm the need for additional research.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, one skilled in the pharmaceutical arts would have an undue burden to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles above, indicates the requirement for undue

experimentation. The ability of an agent that treats all conditions construed by the claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claim. Undue experimentation will be required to practice Applicants' invention.

Sitrick v. Dreamworks LLC, 85 USPQ2d 1826, 1830 (Fed. Cir. 2008) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable all of the embodiments. "Because the asserted claims are broad enough to cover both [embodiments], the [specification] must enable both embodiments." Here, the claims at issue cover many embodiments and do not enable any of them.

Automotive Tech. Int'l. v. BMW of N. America, Inc., 84 USPQ2d 1108, 1116 (Fed. Cir. 2007) decided that a claim is not enabled when the claim covers multiple embodiments but the specification fails to enable one of the embodiments. "Thus, in order to fulfill the enablement requirement, the specification must enable the full scope of the claims that includes both [embodiments], which the specification fails to do." Here, the claims at issue cover many embodiments and do not enable any of them.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 36-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36:

- The recitation of a "metabolite" fails to particularly point out and distinctly claim the intended subject matter. Metabolites are any intermediates and any products of metabolism. A primary metabolite may be directly involved in normal growth, development and reproduction. A secondary metabolite is not usually directly involved in those processes, but may have some type of unknown ecological function.

Claims 37-43:

The recitation of modulation of *in vivo* activity of a kinase, where the kinase is p70S6K, inhibiting p70S6K, treating any disease or disorder associated with uncontrolled, abnormal or unwanted cellular activities, screening for a p70S6 kinase modulator, inhibiting cell proliferative activity or inhibiting abnormal cell metabolic activity fail to particularly point out and distinctly claim the intended subject matter. It is not possible to determine exactly what these terms encompass and define.

Modulate kinase activity *in vivo*. Kinases (phosphotransferase) are enzyme types that transfer phosphate groups from high-energy donor molecules, e.g., ATP, to specific target molecules (substrates); the process is termed *phosphorylation*. An enzyme that *removes* phosphate groups from targets is known as a phosphatase. One of the largest kinase groups are protein kinases, which act on and modify activity of specific proteins, transmit signals and control complex cell processes. Up to 518

different human kinases have been identified. Various other kinases act on small molecules (lipids, carbohydrates, amino acids, nucleotides, and more), either for signaling or to prime them for biochemical reactions in metabolism.

Modulate p70S6K activity *in vivo*. p70S6K participates in protein synthesis control and activates in response to hormones, mitogens and nutrients. It phosphorylates the 40S ribosomal protein S6, which is involved in translation of certain mRNAs, the 5'-TOP mRNAs encoding ribosomal proteins and elongation factors. p70S6K is activated by insulin in muscle, but not in hepatocytes. In these cells, p70S6K is activated by amino acids like glutamine and leucine, which act synergistically. However, crosstalk between insulin and amino acids can be demonstrated with leucine, which enhances insulin signaling towards p70S6K in many cell types, including hepatocytes.

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control energy-consuming biosynthetic pathways, are less active when ATP supply becomes limiting. The effect of different AMPK activators and the effect of protein phosphatase inhibitors on the amino-acid-induced ACC and p70S6K activation were examined in freshly prepared rat hepatocytes. Results show that ACC and p70S6K activation depend on protein phosphatase and both enzymes may be inactivated under conditions leading to AMPK activation.

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Conjugated linoleic acid may act by antioxidant mechanisms, prooxidant cytotoxicity, inhibition of nucleotide and protein synthesis, reduction of cell proliferative activity and inhibition of both DNA-adduct formation and carcinogen activation. In male Syrian hamsters, stress influences epidermal cell proliferative activity and sebaceous gland activity.

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Allowed Claims

Claims 13-20, 29, 34 and 35 are allowed. An examiner's statement of reasons for allowance can be found in the previous Office Action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

Cecilia M. Jaisle